REMARKS

Claims 1, 2, and 19-32 were pending. In the Office Action dated July 9, 2004, the Examiner withdrew claims 26, 27, 31, and 32 from consideration as drawn to a non-elected species. Applicants have herein amended claims 1, 19, and 24; cancelled claims 20 and 28-32; and added claims 33 and 34. Support for the amendments and the new claims can be found throughout the specification, e.g., at page 1, lines 5-10; page 5, lines 5-24; page 6, lines 16-19; page 15, lines 13-23; page 58, lines 11-27; page 60, lines 19-25; page 61, lines 14-19; page 61, line 20 – page 62, line 23; page 62, line 24 – page 63, line 10; and the results set forth on pages 63-65, including Tables 1-3. No new matter has been added. Accordingly, claims 1, 2, 19, 21-25, and 33-34 are pending.

In light of the amendments and the remarks set forth herein, Applicants respectfully request reconsideration and allowance of all pending claims.

Request for Replacement 1449 Form

Pursuant to the Examiner's request, Applicants have provided a replacement 1449 form copied from the Information Disclosure Statement submitted on June 30, 2003. Applicants respectfully request that the Examiner initial and sign the replacement 1449 form.

Substitute Sequence Listing

The Examiner objected to claim 25, stating that the sequence listing identified SEQ ID NO: 32, 34, and 36 as identical to SEQ ID NO: 20, 27, and 35, respectively. Applicants provide a Substitute Sequence Listing herein correcting the errors in the sequences identified for SEQ ID NOs: 32, 34, and 36. As can be seen from amended Table 3[1], SEQ ID NOs: 32, 34, and 36 are not identical to SEQ ID NO: 20, 27, and 35, but rather include an acetylated proline at the N-terminus. The Substitute Sequence Listing filed herewith corrects these errors. No new matter

[1] See Response and Amendment filed October 26, 2001, amending the specification to conform to the Sequence Listing filed concurrently therewith.

has been added. Accordingly, Applicants respectfully request withdrawal of the objection to claim 25.

Rejections under 35 U.S.C. § 112

The Examiner rejected claims 19, 24, and 29 under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Examiner asserted that the recitation of "SH2-pY interactions" was vague and indefinite because it was unclear:

> if said interaction refers to the interaction of the unphosphorylated SH2 domains of STAT with phosphorylated receptor, or if this interaction refers to the interaction between the phosphorylated SH2 domains of STAT with other STAT molecules to form homo- or heterodimers, or if this interaction involves the binding of tyrosine phosphorylated STAT to DNA.

See Office Action dated July 9, 2004 at page 3.

Applicants respectfully disagree with respect to the claims as amended. The amended claims recite that the SH2-pY interactions are between the SH2 domain of one STAT polypeptide monomer and a pY on another STAT polypeptide monomer. Accordingly, Applicants assert that claims 19 and 24 are clear and definite and request withdrawal of the rejections under 35 U.S.C. § 112, second paragraph.

The Examiner also rejected claim 20 under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. Applicants have herein cancelled claim 20, thereby rendering the rejection moot. Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

Rejections under 35 U.S.C. § 103

The Examiner rejected claims 1, 2, 19, 28, 29, and 30 under 35 U.S.C. § 103(a) as being unpatentable over Han *et al.* (Oncology Research, 1997, Vol. 9, pp. 581-587) ("Han") and Zushi *et al.* (International Journal of Cancer, 1998, Vol. 78, pp. 326-330)

("Zushi") as evidenced by Ihle and Kerr (Trends in Genetics, 1995, Vol. 11, pp. 69-74) ("Ihle"). In particular, the Examiner stated that Han teaches that ethyl-2,5-dihydroxy cinnamate inhibited the tyrosine kinase activity of EGF receptor and that "it would be inherent that STAT3 activation would be inhibited because the phosphorylation of the EGF receptor is inhibited;" that Zushi teaches that the EGF receptor AG1478 effectively suppressed the activation of STAT3; and that Ihle teaches that inhibition of the tyrosine phosphorylation of STAT inhibits dimerization of STAT. In sum, the Examiner asserted that it would have been obvious at the time of the invention to administer ethyl-2,5-hydroxycinnamate or AG1478 to patients with glioblastoma, as one of skill in the art would have been motivated to do so by the suggestion of Han that the inhibition of EGF tyrosine kinase activity be used as a method of treating glioblastoma.

Applicants respectfully disagree with respect to the claims as currently amended. Proper analysis under § 103 requires consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed product or carry out the claimed process, and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have had a reasonable expectation of success. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Amended claim 1 recites a method of inhibiting growth of cancer cells in a patient. The method includes administering to the patient an effective amount of an antagonist of STAT (signal transducer and activator of transcription) signaling, where the antagonist antagonizes STAT homodimer DNA binding and where the antagonist noncovalently binds to a STAT polypeptide. At no point do the Han, Zushi, or Ihle references teach or suggest, either alone or in combination, a method of inhibiting the growth of cancer cells that includes administering a STAT antagonist that noncovalently binds to a STAT polypeptide. Han and Zushi teach antagonists of the EGF receptor that inhibit phosphorylation of the EGF receptor and perhaps bind noncovalently to the EGF receptor. There is simply no teaching or suggestion to administer an antagonist of STAT signaling where the antagonist noncovalently binds to a STAT polypeptide. Moreover, the references provide no teaching or suggestion to modify an

antagonist of an EGF receptor such that it would be able to bind noncovalently to a STAT polypeptide. Accordingly, Applicants respectfully assert that the claims are not obvious given the cited references, and request withdrawal of the rejections under 35 U.S.C. § 103.

The Examiner rejected claims 1, 2, 19, 28, 29, and 30 under 35 U.S.C. § 103 as unpatentable over Nielsen *et al.* (PNAS, 1997, Vol. 94, pp. 6764-6769) ("Nielsen") as evidenced by Ihle. In particular the Examiner stated that Nielsen teaches that AG490 inhibits the phosphorylation of STAT3, which, as taught by Ihle, would inhibit dimerization of STAT3 and/or disrupt normal SH2-pY interactions.

Applicants respectfully disagree with respect to the claims as amended. As indicated above, the present claims recite that an antagonist of STAT signaling for use in the methods bind noncovalently to a STAT polypeptide. Neither Nielsen nor Ihle teach or suggest such an antagonist. Nielsen teaches that AG490 inhibits Jak kinase and, as such, perhaps binds noncovalently to Jak kinase. Neither of the cited references teaches or suggests that one having ordinary skill in the art should modify the AG490 Jak kinase inhibitor so that it would bind noncovalently to a STAT polypeptide, nor do they provide any suggestions as to the modifications necessary to achieve such a result. Accordingly, Applicants respectfully assert that the claims are not obvious given the cited references, and request withdrawal of the rejections under 35 U.S.C. § 103.

The Examiner rejected claims 1, 19, 28, and 29 under 35 U.S.C. § 103(a) as being unpatentable over Wasik *et al.* (Leukemia and Lymphoma abstract, 1998 Feb., Vol. 28, pp. 551-560) ("Wasik") as evidenced by Ihle. In particular, the Examiner stated that Wasik teaches that the compounds CT2576 and CT5589 inhibit the tyrosine phosphorylation of STAT5.

Applicants respectfully disagree. As indicated above, the amended claims recite that an antagonist of STAT signaling bind noncovalently to a STAT polypeptide. Wasik teaches that CT2576 and CT5589 are inhibitors of IL-2 signaling and inhibit

phosphorylation of the downstream elements STAT5 and Jak3. There is no teaching or suggestion in Wasik of the use of antagonists that noncovalently bind to a STAT polypeptide for inhibiting the growth of cancer cells, or of particular modifications to make to the CT2576 and CT5589 molecules to result in such antagonists. Accordingly, Applicants respectfully assert that the claims are not obvious and request withdrawal of the rejections.

The Examiner rejected claims 1, 2, 19, 21-25, 29, and 30 under 35 U.S.C. § 103(a) as being unpatentable over Grigorieva *et al.* (Blood, 1996, Vol. 88, No. 10, suppl. 1, part 1-2, page 104A) ("Grigorieva"); Yu *et al.* (Journal of Immunology, 1997, Vol. 159, pp. 5206-5210) ("Yu"); Sartor *et al.* (Cancer Research, 1997, Vol. 57, pp. 978-987) ("Sartor"); Garcia *et al.* (Cell Growth and Differentiation, 1997, Vol. 8, pp. 1267-1276) ("Garcia"); and Frank *et al.* (Journal of Clinical Investigation, 1997, Vol. 100, pp. 3140-3148) ("Frank") in view of Fukada *et al.* (Immunity, 1996, Vol. 5, pp. 449-460) ("Fukada"); Caldenhoven *et al.* (The Journal of Biological Chemistry, 1996, Vol. 271, pp. 13221-1227) ("Caldenhoven"); Horvath *et al.* (Genes and Development, 1995, Vol. 9, pp. 984-994) ("Horvath"); and Nakajima *et al.* (EMBO, 1996, Vol. 15, pp. 3651-3658) ("Nakajima"). In particular, the Examiner stated that Frank, Grigorieva, Yi, Sartor, and Garcia teach the constitutive phosphorylation of STAT3 in transformed and cancerous cells. The Examiner acknowledged that none of Frank, Grigorieva, Yi, Sartor, and Garcia teach the administration of a peptide that would bind to the SH2 domain of STAT3 or disrupt the SH2-phosphotyrosine interaction as a therapeutic intervention against cancer. The Examiner further stated that Caldenhoven teaches that the STAT3 beta splice is a dominant negative mutant that exhibits competitive inhibition of binding to the pIRE site by, e.g., formation of heterodimers with wild type STAT3. With respect to Horvath, the Examiner stated that Horvath taught mutations in the DNA binding domain of STAT1 and STAT3 that led to reduced DNA binding affinity of mutant homodimers and heterodimers with wild type STAT1 or STAT3. Finally, with respect to

Nakajima, the Examiner stated that the reference teaches that certain STAT3 mutants could function as dominant negative mutants by formation of heterodimers with wild type STAT3 that do not bind the DNA target. In conclusion, the Examiner stated that it would have been *prima facie* obvious at the time the invention was made "to administer a STAT3 mutant that was defective in DNA binding or which decreased the transcriptional activation by STAT3 by binding to wild-type STAT3 . . .to overcome the constitutive activation of STAT3."

Applicants respectfully disagree with respect to the claims as amended. Claim 1 recites that an antagonist for use in the method antagonize STAT homodimer DNA binding. At no point do any of the cited references, either or alone in combination, teach or suggest such an antagonist. None of the Frank, Grigorieva, Yi, Sartor, or Garcia references teach or suggest any STAT antagonist, let alone a STAT antagonist that antagonizes STAT homodimer DNA binding. While the Caldenhoven, Horvath, and Nakajima references teach that heterodimers of a STAT mutant with a wild type monomer can exhibit reduced DNA binding, none of the references teach or suggest that such mutants can antagonize the binding of a wild type STAT homodimer to DNA. Moreover, one having ordinary skill in the art would have no reasonable expectation of success in preparing such an antagonist based on the teachings of Caldenhoven, Horvath, and Nakajima regarding antagonism of DNA binding through a mechanism of heterodimer formation. Accordingly, Applicants respectfully assert that the claims are not obvious and request withdrawal of the rejections.

The Examiner rejected claims 1, 2, 19, 24, 25, and 28-30 under 35 U.S.C. § 103(a) as being unpatentable over Grigorieva, Yu, Sartor, Garcia, and Frank in view of Fukada, Zushi *et al.* (International Journal of Cancer, 1997, Vol. 78, pp. 326-330) ("Zushi"), and Horvath. As above, the Examiner stated that Frank, Grigorieva, Yi, Sartor, and Garcia teach the constitutive phosphorylation of STAT3 in transformed and cancerous cells. With respect to Fukada, the Examiner asserted that the reference

teaches the expression of dominant negative STAT3 mutants having tyrosine mutations that prevent phophorylation (and potentially dimerization) of STAT3 polypeptides and that caused cells to undergo apopotosis. The Examiner stated that Zushi teaches that a dominant-negative STAT3 tyrosine mutant induced apopotic cell death. Finally, the Examiner stated that Horvath teaches that certain tyrosine mutations in STAT3 block phosphorylation, dimerization, and subsequent DNA binding. In conclusion, the Examiner stated that it would have been *prima facie* obvious at the time the invention was made to administer a STAT3 mutant that was defective in tyrosine phosphorylation as a dominant negative mutant.

Applicants respectfully disagree. As indicated above, claim 1 recites that an antagonist for use in the method antagonize STAT homodimer DNA binding. At no point do any of the cited references, either or alone in combination, teach or suggest such an antagonist. None of the Frank, Grigorieva, Yi, Sartor, or Garcia references teach or suggest any STAT antagonist, let alone a STAT antagonist that antagonizes STAT homodimer DNA binding. While the Fukada, Zushi, and Horvath references teach that STAT tyrosine mutants possibly exhibit reduced homodimerization and lead to the induction of apoptosis, none of the references teach or suggest that such mutants can antagonize the binding of a wild type STAT homodimer to DNA. Moreover, one having ordinary skill in the art would have no reasonable expectation of success in preparing such an antagonist based on the teachings of Fukada, Zushi, and Horvath regarding antagonism of DNA binding through a mechanism of reduced mutant homodimer formation. Accordingly, Applicants respectfully assert that the claims are not obvious and request withdrawal of the rejections.

CONCLUSION

Given all of the above, Applicants respectfully assert that all claims are in condition for allowance, which action is requested. The Examiner is invited to telephone the under-signed if such would expedite prosecution.

Enclosed is a $225.00 check for the Petition for Extension of Time fee (two months). Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

Date: 12/9/04

Teresa A. Lavoie, Ph.D.
Reg. No. 42,782

Fish & Richardson P.C., P.A.
60 South Sixth Street
Suite 3300
Minneapolis, MN 55402
Telephone: (612) 335-5070
Facsimile: (612) 288-9696

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Mailed: 6/30/03

ATTY. DOCKET NO.	APPLICATION NO.
10873-008-999	09/492,764

LIST OF REFERENCES CITED BY APPLICANT
(Use several sheets if necessary)

APPLICANT: Jove et. al.

FILING DATE	GROUP
January 27, 2000	1642

U.S. PATENT DOCUMENTS

*EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
	AA	5,716,622	2/10/98	Darnell et. al.			
	AB	5,883,228	3/16/99	Darnell et. al.			
	AC	5,976,835	11/2/99	Darnell et. al.			
	AD	6,265,160	7/24/01	Leonard, W.			
	AE	10/383,707		Yu et al.			3/7/03
	AF	10/380,020		Yu et al.			3/7/03

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION	
							YES	NO
	AG	WO 98/30688	7/16/98	PCT				
	AH	WO 98/41090	9/24/98	PCT				
	AI	WO 99/28465	6/10/99	PCT				
	AJ	WO 00/44774	8/3/00	PCT				
	AK	WO 02/20032	3/14/02	PCT				

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	BP	Nelson et al., 1998, "Activation of STAT3 by the c-Fes protein tyrosine kinase", *J. Biol. Chem.* 273:7072-7077.
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	BU	Sasse et al., 1997, "Mutational Analysis of Acute-Phase Response Factor/Stat3 Activation and Dimerization", *Mol. Cell. Biol.* 17(8):4677-4686.
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	CD	Wang et al., 2000, "Activation of Stat3 preassembled with platelet-derived growth factor-beta receptors requires Src kinase activity", *Oncogene* 19:2075-2085.
	CE	Whitmarsh et al., 1998, "A Mammalian Scaffold Complex that Selectively Mediates MAP Kinase Activation", Science 281: 1671-1674.
	CF	Yu et al., 1997, "Constitutive activation of the JAK-STAT pathway in T lymphoma overexpressing the Lck protein tyrosine kinase", *J. Immunol.* 159:5206-5210.
	CG	Yu et al., 1995, "Enhanced DNA-Binding Activity of a Stat3-Related Protein in Cells Transformed by the Src Oncoprotein", Science 269: 81-83.
	CH	Zhang Y. et al., 2000, "Activation of Stat3 in v-Src transformed fibroblasts requires cooperation of Jak1 kinase activity", J. Biol. Chem. 275:24935-24944.
	CI	Zong et al., 1996, "Unique Signal Transduction of Eyk: Constitutive Stimulation of the JAK-STAT Pathway by an Oncogenic Receptor-type Tyrosine Kinase", EMBO J. 15: 4515-4525.

EXAMINER	**DATE CONSIDERED**

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with **MPEP 609**; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.